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EXAMINER	
LEE, BETTY L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,540	DAVID, NATHANIEL E.	
	Examiner	Art Unit	
	Betty Lee, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 39-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-38 and 57-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed December 13, 2005 is acknowledged. Applicant's election of Group II, claims 20-38 and 58-72 without traverse is noted. Applicant's election of TNF-alpha as the species without traverse is acknowledged. Claims 1-19, 39-57 are withdrawn from consideration. Claims 20-38 and 58-72 are under examination.

Claim Objections

Claims 27 and 62 are objected to because of the following informalities: The claims encompass nonelected species. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

1. Claims 20-38, 58-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for dermal color alteration treatment by laser therapy in conjunction with administration of macrophage colony stimulating factor (MCSF, a cytokine), does not reasonably provide enablement for a method for altering coloration by administering an effective amount of a cytokine or a tumor necrosis factor e.g. TNF-alpha in the absence of laser therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method for altering coloration of a dermal region comprising administering to said region an effective amount of a cytokine or a tumor necrosis factor, e.g. TNF-alpha wherein the dermal region comprises a tattoo. The invention is also drawn to administration of TNF-alpha in conjunction with laser therapy as a color alteration treatment.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that keratinocytes express and secrete both tumor necrosis factor-α and transforming growth factor-β, which act as paracrine inhibitors of human melanocyte proliferation and melanogenesis (Sohn, *et al.* Dermat. Surg.30: 898-907, 2004). Sohn, *et al* teach that Q-switch-mode laser treatment of congenital nevi does not result in complete histological clearance, and many patients have partial repigmentation within several months (pg 898, Abstract). Sohn, *et al* teach that down-regulation of E-cadherin and TNF-alpha may induce the proliferation of melanocytes, resulting in the formation of recurrent pigmented macules (RPMs) (pg 898, Abstract). Therefore, the art teaches that other factors such as E-cadherin may be involved in pigmentation and administering TNF-a alone prior to or post laser therapy may not achieve the desired effect.

The amount of direction or guidance present and the presence or absence of working examples: The specification does not disclose any working examples of

cytokines or TNF-alpha for successfully altering coloration in dermal regions. The specification fails to provide any guidance as to how the cytokine or tumor necrosis factor work when administered topically, subcutaneously or transdermally on dermal regions comprising a traumatic, decorative or gunpowder tattoo.

The breadth of the claims and the quantity of experimentation needed: The claims are directed to a broad spectrum of cytokines, which includes TNF-alpha for color alteration treatment prior to or post laser therapy for tattoo removal. However since the art teaches that there is considerable unpredictability in factors involved in pigmentation and proliferation of melanocytes, it would require undue experimentation for a person of skill in the art to be able to use the invention as described.

Claims 20-38 and 58-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117).

A review of the language of the claim indicates that these claims are drawn to a genus, i.e., cytokines excluding macrophage colony-stimulating factor.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* TNF-α. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of which comprises cytokines excluding macrophage colony-stimulating factor. The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-21, 26-37, 58, 59, 61-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen, *et al* (Medical Hypotheses 45: 83-85, 1994) in view of Jimenez-Cervantes, *et al* (J. Cell Sci. 114: 2335-2344, 2001) and Solis, *et al* (Dermatol. Surg. 28:83-87, 2002).

The claimed invention is drawn to a method for altering coloration of a dermal region comprising administering to said region an effective amount of a cytokine or a tumor necrosis factor, e.g. TNF-alpha wherein the dermal region comprises a tattoo. The invention is also drawn to administering the cytokine or TNF-alpha prior to or post laser therapy.

Cohen, *et al* teach the adjuvant use of macrophage colony stimulating factor (MCSF), a cytokine stimulating growth and differentiation of mononuclear phagocytes, in tattoo removal using laser surgery. Cohen, *et al* teach that following laser irradiation, the dermis experiences photo-induced 'thermolysis' and the altered pigment is engulfed by macrophages (pg 84, col 1). Cohen, *et al* further teach that MCSF is administered by injections on days one through five and eight through twelve (pg 84, col 1) and gives the protocol for administering cytokine prior to laser therapy. Cohen, *et al* teach that the recruitment of additional macrophages has an essential role in the removal of tattoo pigment (pg 85, col1). Cohen,*et al* do not teach the administration of TNF-α for color alteration.

Jimenez-Cervantes, *et al* teach that H_2O_2 is formed in the mammalian skin as a byproduct of melanin synthesis and following UV irradiation (pg 2335, Abstract). Jimenez-Cervantes, *et al* teach that H_2O_2 acts as an intracellular second messenger for TNF-α and TGF-β, two cytokines shown to exert a strong inhibition of melanogenesis (pg 2341, col 2). In addition, Jimenez-Cervantes, *et al* teach that the hypopigmenting cytokines TGF-β and TNF-α decrease the half-life of enzymatically active tyrosinase in B16 melanocytes (pg 2342, col 2, 1st prgh).

Solis, *et al* teach that lasers such as Q-switched alexandrite laser, Q-switched ruby laser and Nd:YAG laser have been used for specific removal of tattoos (pg 83, col 1). Solis, *et al* teach the topical use of imiquimod, an immune response modifier, for tattoo removal (pg 85, col 2). In addition, Solis, *et al* teach that imiquimod exerts its

action by activation of the innate immune response due to the production of cytokines, including IFN-α and TNF-α (pg 85, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of TNF-α as an adjuvant in laser therapy as taught by Cohen, *et al* and Jimenez-Cervantes, *et al* because TNF-α is a hypopigmenting cytokine and therefore beneficial for a color alteration treatment. The person of ordinary skill in the art would have been motivated to modify the teachings of Solis, *et al* by administering TNF-α for tattoo removal because TNF-α has a strong inhibitory effect on the formation of melanin which causes dermal pigmentation.

Claims 20-25, 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen, *et al* (Medical Hypotheses 45: 83-85, 1994) and Jimenez-Cervantes, *et al* (J. Cell Sci. 114: 2335-2344, 2001) in view of Beade, *et al* (Am. J. Clin. Dermatol. 2(1): 21-25, 2001).

The claimed invention is drawn to a method for altering coloration of a dermal region comprising administering to said region an effective amount of a cytokine or a tumor necrosis factor wherein the dermal region comprises a decorative tattoo, a traumatic tattoo or a gunpowder tattoo.

As set forth *supra*, Cohen, *et al* teach the adjuvant use of macrophage colony stimulating factor (MCSF), a cytokine stimulating growth and differentiation of mononuclear phagocytes, in tattoo removal using laser surgery. Cohen, *et al* do not teach the different tattoos.

As set forth *supra*, Jimenez-Cervantes, *et al* teach that H_2O_2 acts as an intracellular second messenger for TNF-α and TGF-β, two cytokines shown to exert a strong inhibition of melanogenesis (pg 2341, col 2). Melanin causes pigmentation in the skin or dermal regions.

Beade, *et al* teach that decorative amateur tattoos respond well to laser treatment (pg 23, col 1). Beade, *et al* teach that traumatic tattoos occur following different types of injury to the skin, e.g. gunpowder and particulate matter, and three lasers such as as Q-switched alexandrite laser, Q-switched ruby laser and Nd:YAG laser have been used for specific removal of tattoos (pg 23, col 2). In addition, Beade, *et al* teach that localized and generalized allergic reactions occur following tattoo removal with the Q-switched ruby and Nd:YAG lasers (pg 24, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of TNF-α as an adjuvant in laser therapy as taught by Cohen, *et al* and Jimenez-Cervantes, *et al* because TNF-α is a hypopigmenting cytokine and therefore beneficial for a color alteration treatment. The person of ordinary skill in the art would have been motivated to modify laser treatments for the different tattoos removal as taught by Beade, *et al* by administering TNF-α for color alteration because TNF-α has a strong inhibitory effect on the formation of melanin which causes dermal pigmentation.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5: 30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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